Applicants respectfully request this ground of rejection be held in abeyance pending resolution of the remaining issues.

Rejection Under 35 U.S.C. § 112, First Paragraph (Enablement)

Claim 1 has been rejected under 35 U.S.C. § 112, first paragraph, as not being enabled by the Specification. According to the Examiner, the Specification is enabling for claims limited to plant transformation with the native barley fructosyltransferase gene or mutant bacterial fructosyltransferase genes for the production of oligosaccharides, but does not provide enablement for claims directed to (1) plant fructosyltransferase genes from any species other than barley, (2) mutant plant fructosyltransferase genes, or (3) any other enzymes capable of converting sucrose to oligosaccharides. The Examiner states that undue experimentation would be required to identify a multitude of non-exemplified enzymes involved in oligosaccharide synthesis, to identify and isolate the genes encoding them, and to evaluate the genes for their ability to confer oligosaccharide-synthesizing activity to transgenic plants. Applicants respectfully disagree.

Claim 1 is directed to a method for producing oligosaccharides, wherein the first step comprises selecting a gene which codes for an enzyme that is capable of converting sucrose into an oligosaccharides. The Specification describes simple *in vivo* and *in vitro* assays for activities that convert sucrose into oligosaccharides, as described, for example, on page 13, lines 19-30. According to one *in vitro* assay, the sample being assayed for oligosaccharide-producing activity is incubated with 200 mM sucrose, and the reaction products are separated by means of thin-layer chromatography and made visible using a fructose-specific reagent. The success of these in vitro assays both for identifying and for purifying activities that convert sucrose into oligosaccharides is well-documented throughout the Specification. Using such assays, applicants purified oligosaccharide-producing activities encoded by the *ftf* gene of *Streptococcus mutans* (Specification, page 13, lines 19-30; FIGURE 1), and oligosaccharide-producing activities from

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onion (Specification, page 17, lines 3-28; FIGURE 4), barley (Specification, page 19, line 4 to page 21, lines 25-66), and Jerusalem artichoke (Specification, page 28, lines 3-9). Thus, the Specification provides abundant and detailed guidance to enable one of skill in the art to identify and purify activities that convert sucrose into oligosaccharides. Therefore, no undue experimentation would be required for one of skill in the art to use the teachings of the Specification to identify and purify activities that convert sucrose into oligosaccharides.

The Specification also describes the identification and isolation of genes coding for oligosaccharide-producing activities. For example, the source of an enzymatic activity producing oligosaccharides from glucose in an *in vitro* assay was identified as the *ftf* gene (Specification, page 13 lines 19-30). The Specification also provides a detailed description of the identification of the gene encoding an oligosaccharide-producing activity (6-SFT) in barley (Specification, page 23, line 14 to page 26, line 26). Thus, the Specification describes a method for determining the N-terminal amino acid sequence of the purified oligosaccharide-producing activity (page 23, lines 14 to 26), a strategy for obtaining a cDNA clone coding for 6-SFT (FIGURE 10), the design of a probe generated by reverse transcription polymerase chain reaction based on the amino acid sequences (Specification, page 23, line 27 to page 24, line 11), methods for making a cDNA library by extracting total RNA from leaves and for screening the cDNA library with the probe to identify positive clones (Specification, page 24, line 13 to page 25, line 18), and the determination of the sequence of positive clones (Specification, page 25, lines 18-33 (FIGURE 11; SEQ ID NO:1). The Specification also describes that similar methods were used to identify and isolate the gene coding for an oligosaccharide-producing enzyme from onion seed (Specification, page 17, line 2 to page 18, line 2) and from Jerusalem artichoke (Specification, page 28, lines 3-19).

Finally, the Specification also describes that genes from micro-organisms or plants that code for oligosaccharide-producing activities may be selected from previously-identified

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naturally-occurring mutants (Specification, page 7, lines 1-4), and that genes coding for fructosyltransferases may be modified by targeted or random mutagenesis to provide enzymes having the desired oligosaccharide-synthesizing enzymatic properties (Specification, page 6, lines 21-23; page 7, lines 1-3; page 15, lines 4-6). For example, the Specification provides a simple *in vivo* assay for identifying mutant enzymes that produce trisaccharides but not polysaccharides. According to this assay, the coding sequences for an enzyme having fructosyltransferase activity are expressed in a bacterial cells, such as cyanobacterial cells, that become sucrose-sensitive as a result of polymer accumulation in the periplasm. These cells are then exposed to a mutagen, which introduces point mutations, and mutants that become sucrose-resistant are selected and further characterized using an *in vitro* assay as described above. Using this assay, applicants have identified mutant *ftf* enzymes which only produce trisaccharides (Specification, page 6, lines 6-11; page 14, line 10 to page 15, line 6). Guidance for making targeted mutations is also provided in the Specification, for example, by comparing conserved amino acid sequences between vegetable, fungal, and bacterial enzymes with similar activities (Specification, page 26, lines 13-26; FIGURES 12 and 13). The identification of at least five well-conserved domains, provides an effective framework to identify, isolate, and evaluate genes coding for oligosaccharide-producing activities using well-established methods.

As described above, the Specification provides detailed guidance and direction for identifying and purifying oligosaccharide-producing activities from micro-organisms and plants, and for identifying and isolating the genes coding for these activities. Therefore, no undue experimentation would be required of one of ordinary skill in the art to identify and isolate genes coding for oligosaccharide-producing activities, as recited in Claim 1.

The Examiner states that the isolation, identification, and characterization of fructosyltransferase genes is unpredictable because (1) the biosynthesis and degradation of fructan occurs only in a limited number of plant species, (2) the genes encoding two microbial

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enzymes possess complex regulation and complex expression products which are not completely understood, and (3) substitution of a single amino acid completely alters the activity of a fructosyltransferase. Applicants respectfully disagree.

First, the absence of oligosaccharide-producing activities from many plant species does not render the isolation of fructosyltransferase genes from other species unpredictable. Claim 1 is directed to selecting genes coding for an enzyme which is capable of converting sucrose into an oligosaccharide. It is not directed to selecting such genes from all plant species. One of skill in the art would not attempt to purify an oligosaccharide-producing activity from a plant species that has not been shown to possess such an activity. The Specification clearly describes *in vitro* and *in vivo* assays for identifying an activity that produces fructans from sucrose, as described above. In addition, the Specification provides a detailed description of methods for identifying and isolating genes encoding such activities, as described above. Moreover, the cloning of the 6G-FFT from onion using the barley 6-SFT sequence described in the Specification as a probe further demonstrates the predictability of isolating additional genes coding for oligosaccharide-producing activities based on the information provided in the Specification (Vijn et al. (1997) *The Plant Journal* 11(3):387-398).

Second, the complexity of the regulation and expression products of two microbial fructosyltransferases does not render the isolation of genes coding for oligosaccharide-producing activities unpredictable. The Specification describes several assays that can be used for isolating only those activities, and genes coding for those activities, that produce oligosaccharides from sucrose. The Specification also describes the separation of desirable activities from undesirable activities in a complex mixture (Specification, page 21, line 27 to page 22, line 5). Finally, the Specification describes methods for modifying the activities of enzymes using mutagenesis. Using such a method, applicants have modified an enzyme that produces oligosaccharides in

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addition to high-molecular weight fructans to create an enzyme that produce only trisaccharides. (Specification, page 6, lines 6-11; page 14, line 10 to page 15, line 6).

Third, the fact that a single amino acid substitution can completely alter the activity of a protein does not make the substitution of sequences in fructosyltransferase genes unpredictable. In contrast, knowledge of activity-altering mutations in one fructosyltransferase gene provides a method for predicting how the activity of other fructosyltransferases can be altered and permits the rational design of enzymes having desirable activities and lacking undesirable activities. For example, a gene coding for an enzyme producing both oligosaccharides and high-molecular weight fructans (such as the *ftf* gene in *S. mutants*) may be modified by targeted mutations to encode an enzyme producing only oligosaccharides (such as the mutant *ftf* gene described in the Specification, for example, at page 14, lines 10-30).

Accordingly, the quantity of experimentation necessary to select appropriate genes coding for enzymes capable of converting sucrose into an oligosaccharide is relatively small. The Specification provides adequate direction and guidance for the identification of oligosaccharide-producing enzymes and for the isolation of the genes coding for them, as described above. Working examples are also provided for one microbial gene and three plant genes. Moreover, the prior art is well-versed in the identification and isolation of genes based on partial amino acid sequences of biochemical activities. Therefore, the breadth of the claims is commensurate with the disclosure in the Specification. For all these reasons, it would not require no undue experimentation for one of ordinary skill in the art to practice the invention recited in Claim 1. Accordingly, applicants respectfully request withdrawal of this ground of rejection.

Rejection Under 35 U.S.C. § 112, First Paragraph (Written Description)

The Examiner has rejected Claim 1 under 35 U.S.C. § 112, first paragraph, as not having an adequate written description to convey that the applicants had possession of the claimed

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invention. The Examiner states that the Specification fails to provide an adequate written description of the broadly claimed genus because it only provides guidance for the isolation and characterization of barley and bacterial fructosyltransferase genes. Further, the Examiner cites *University of California v. Eli Lilly*, 43 U.S.P.Q.2d (Fed. Cir. 1997) as holding that a description of a protein sequence from an organism fails to provide an adequate written description of the cDNA sequence coding for it, despite the disclosure of a cDNA encoding that protein from another organism. Applicants respectfully disagree.

First of all, applicants are not claiming nucleotide sequences, as was the case in *Eli Lilly*. Applicants are claiming methods of producing oligosaccharides in transgenic plants by expressing enzymes in plants capable of converting sucrose into oligosaccharides. Therefore, applicants are required to provide an adequate written description of methods of producing oligosaccharides in plants. They are not required to provide a written description of cDNA sequences *per se*. It is believed that the Examiner's rejection of Claim 1 as not meeting the written description requirement on the basis of the sufficiency of the disclosure of cDNA sequences is inappropriate and applicants respectfully request withdrawal of this ground for rejection.

Moreover, new case law relating to the written description requirement has emerged from the Federal Circuit since the issuance of the Examiner's Action. In *Enzo Biochem Inc. v. Gen-Probe Inc.*, 63 U.S.P.Q.2d 1609 (Fed. Cir. 2002), the Federal Circuit addressed whether a genus of nucleotide sequences was sufficiently described by three nucleotide sequences to meet the written description requirement. It emphasized that "[c]ompliance with the written description requirement is essentially a fact-based inquiry that will necessarily vary depending on the nature of the invention claimed." *Id.* at 1612. It specifically noted that "[i]t is not correct ... that all functional descriptions of genetic material fail to meet the written description requirement." *Id.* at 1613. It adopted the PTO guidelines which state that the written description requirement may

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be met by "disclosure of sufficiently detailed, relevant identifying characteristics ...*i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." *Id.* at 1613 (*citing* Guidelines, 66 Fed. Reg. at 1106). Thus, the Federal Circuit held that the district court had erred in granting summary judgment that the claims are invalid for failure to meet the written description requirement and remanded for a determination of the factual issue whether the disclosure provided by the three nucleotide sequences, coupled by the skill of the art, adequately describes the claimed genus of nucleotide sequences to satisfy the written description requirement. *Id.* at 1615-1616.

Thus, even if disclosure of multiple genes were required in order for Claim 1 to meet the written description requirement, the disclosure provided by the present application would be adequate. The Specification discloses four species: a microbial gene (from *Streptococcus mutans*) and three plant genes (from barley, onion, and Jerusalem artichoke) coding for oligosaccharide-producing activities. Moreover, the Specification discloses functional characteristics of the proteins encoded by the genes (*i.e.*, converting sucrose to oligosaccharides) and provides assays for measuring this function, as described above. The Specification also provides structure/function correlations in terms of five highly conserved amino acid domains (Specification, FIGURES 12 and 13). In addition, the level of skill in the art is high: in general, one of ordinary skill in the art is a scientist with 6-12 years of training in biotechnology. Therefore, the Specification discloses an adequate number of species in view of the level of skill in the art to satisfy the written description requirement of a claim directed to a genus of genes. However, as pointed out above, Claim 1 is not directed to a genus of genes but rather to methods of producing oligosaccharides in plants. Accordingly, applicants respectfully request withdrawal of this ground of rejection.

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Rejection under 35 U.S.C. §102(b)

Claim 1 has been rejected under 35 U.S.C. § 102(b) as being anticipated by WO 89/12386 (Calgene). According to the Examiner, Calgene teaches tobacco plant transformation with a vector encoding the *B. subtilis sacB* fructosyltransferase gene to accumulate non-degradable carbohydrates. Applicants respectfully traverse this rejection.

Applicants' invention is directed to methods of producing oligosaccharides in plants. As described in the Specification, the expression of the *sacB* gene of *B. subtilis* in plants results in the production of high-molecular weight polysaccharides. WO 89/12386 does not disclose, teach, or suggest the production of oligosaccharides in plants (Specification, page 6, lines 2-5). Therefore, Claim 1 is not anticipated or rendered obvious by WO 89/12386. Accordingly, applicants respectfully request withdrawal of this ground of rejection.

CONCLUSION

In view of the foregoing remarks, Claim 1 is believed to be in condition for allowance. Reconsideration and favorable action is requested.

Respectfully submitted,

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